PATENT COOPERATION TREA

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION See Form PCT/IPEA/416	
LTP-0003.PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/SE 2003/000973	12.06.2003	20.06.2002
International Patent Classification (IPC) or national classification and IPC		
A61K 31/727, A61K 47/44, A61K 9/20		
Applicant		
LTP Lipid Technologies Provider AB et al		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *(sent to the applicant and to the International Bureau)* a total of _____ sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s))
      _____, containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:
   - ☒ Box No. I Basis of the report
   - ☐ Box No. II Priority
   - ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☐ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☒ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
20.01.2004	11.08.2004
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Form PCT/IPEA/409 (cover sheet) (January 2004)

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

national application No.
PCT/SE 2003/000973

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of:

☐ international search (under Rules 12.3 and 23.1(b))
☐ publication of the international application (under Rule 12.4)
☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

☒ the international application as originally filed/furnished

☐ the description:

pages _____ as originally filed/furnished
pages* _____ received by this Authority on _____
pages* _____ received by this Authority on _____

☐ the claims:

pages _____ as originally filed/furnished
pages* _____ as amended (together with any statement) under Article 19
pages* _____ received by this Authority on _____
pages* _____ received by this Authority on _____

☐ the drawings:

pages _____ as originally filed/furnished
pages* _____ received by this Authority on _____
pages* _____ received by this Authority on _____

☐ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/figs _____
☐ the sequence listing *(specify)*: _____
☐ any table(s) related to the sequence listing *(specify)*: _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/figs _____
☐ the sequence listing *(specify)*: _____
☐ any table(s) related to the sequence listing *(specify)*: _____

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

national application No.
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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 29-30

because:

☒ the said international application, or the said claims Nos. 29-30 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

See PCT Rule 67.1.(iv).: Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____ are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. _____

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in the Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

national application No.
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Box No. V **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1-28	YES
	Claims		NO
Inventive step (IS)	Claims		YES
	Claims	1-28	NO
Industrial applicability (IA)	Claims	1-28	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

The claimed invention relates to a solid heparin tablet comprising polar lipids and non-polar lipids and a method of producing it. Examples of polar lipids are glycolipids and phospholipids, e.g. galactolipids and phosphatidylcholine. Examples of non-polar lipids are monoglycerides and triglycerides (palmkernel oil fractions).

This opinion is based on the documents from the international search report. The following documents are considered relevant:

D1: WO 9319737 A1
D2: WO 0191729 A1
D3: US 5082667 A
D4: Lohikangas L. et al. European Journal of Pharmaceutical Sciences 1, 1994, pages 307-312.

D1 relates to a composition containing a lipid system of at least two lipid components where one of the lipid components is polar and the other is non-polar. The pharmaceutically active compound is heparin or a fragment (Fragmin) thereof. A water containing solvent is also included in such an amount that discrete lipid particles are present. Polar lipids can be phospholipids e.g phosphatidylcholine or glycolipids. Non-polar lipids are e.g. mono-, di- or triglycerides. The glycerides have a preferred carbon chain length of between 6 and 12 carbon atoms. The composition can be used for oral administration. See abstract, page 2, paragraph 7, page 3, paragraph 3, page 5 lines 4-6, page 6, lines 1-5, examples 1-7 and 12. In example 12, no water is added except for the water which is included in the added Fragmin-composition.

.../...

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of: Box V

D2 relates to a solid composition containing heparin, a lipid component and a polymer. The lipid component constitutes e.g. mono-,di- or triglycerides having unsaturated fatty acid esters where the fatty acids have 8-18 carbon atoms. Preferred polymers include polyvinyl pyrrolidon and cellulose derivates. The composition can be formed as capsules, pellets, tablets or preferably tablets with an outer cover. The composition is prepared by melt extrusion, e.g at 80-150 degrees Celsius. Water or alcohol can be used as a solvent. See abstract, page 7, lines 7-35, page 17, lines 27-page 18, line 45, page 22, lines 42-43, page 23, lines 4-9, example 5 and the claims.

The claimed composition differs from this known composition in that it comprises both a polar and a non-polar lipid whereas in the known composition no polar lipid is included.

D3 discloses a solid pharmaceutical tablet, which according to example 2, comprises an active ingredient, cottonseed oil, sodium bicarbonate, lecithin, and PEG 300. The tablet is prepared by melting the oil whereafter the active component and sodium bicarbonate is added to the molten oil. Lecithin and PEG are mixed and is thereafter added to the oil mixture. The mixture is sprayed through a spray gun and broken up into fine droplets, which solidify as discrete particles. In example 2, PEG 300 and lecithin are added to the molten suspension. Thus, tablets that contain a polar lipid, a non-polar lipid and an active agent are known from document D3. See abstract, example 2 and claims 1,3,7 and 12.

The claimed composition differs from this known composition in that the active ingredient in D3 is not heparin.

D4 discloses the study of how the relationship between the amount of phosphatidylcholine and the amount of monoacylglycerol in a lipid matrix affects the absorption of low-molecular heparin on Caco-2-cells. No solid composition is disclosed.

.../...

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of: Box V

None of the above mentioned documents discloses a tablet comprising heparin in combination with a continuous lipid component which constitutes at least one polar and at least one non-polar lipid.

Thus, claims 1-28 are novel.

The closest prior art is represented by document D1.

The claimed composition differs from the composition disclosed in D1 in that it is a solid tablet whereas nowhere in D1 is it mentioned that a tablet can be prepared from the composition.

The problem to be solved is to prepare a heparin composition which constitutes a solid tablet comprising heparin or a heparin fragment and a continuous lipid compound comprising at least a polar lipid and a non-polar lipid.

It is known from D3 to prepare a tablet comprising an active agent and a polar lipid and a non-polar lipid. A person skilled in the art who is confronted with the above mentioned technical problem will therefore have an inventive from D3 to prepare a solid heparin tablet with the same beneficial effects as the heparin composition of D1.

Thus, claims 1-9, 14 and 26 lack an inventive step.

The choice of solvent, to add a coat to the tablet as well as the process of claims 15-25 are all considered as being obvious modifications, especially in view of D2, which are not considered to involve any inventive step.

Claims 10-13, 15-25 and 27-28 lack inventive step.

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

The claims are not supported by the description as required by Article 6 PCT, as their scope is broader than justified by the description. The reasons therefore are the following: the terms "polar lipids" and "non-polar lipids" relate to an extremely large number of possible compositions. The claims therefore contain so many options that a lack of clarity and conciseness within the meaning of Article 6 PCT arises.

The breath of the claims should be such that it represents a reasonable generalisation of the examples provided, and such that it is credible that every compound falling within the scope actually provides a solution to the problem underlying the invention.

Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT are to be found only for the polar lipd being a glycolipid or a phospholipid and a non-polar lipid being a monoglyceride or a triglyceride.